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De synthese van zuurstofchlorides en peptiden met behulp van alpha-chloorethers

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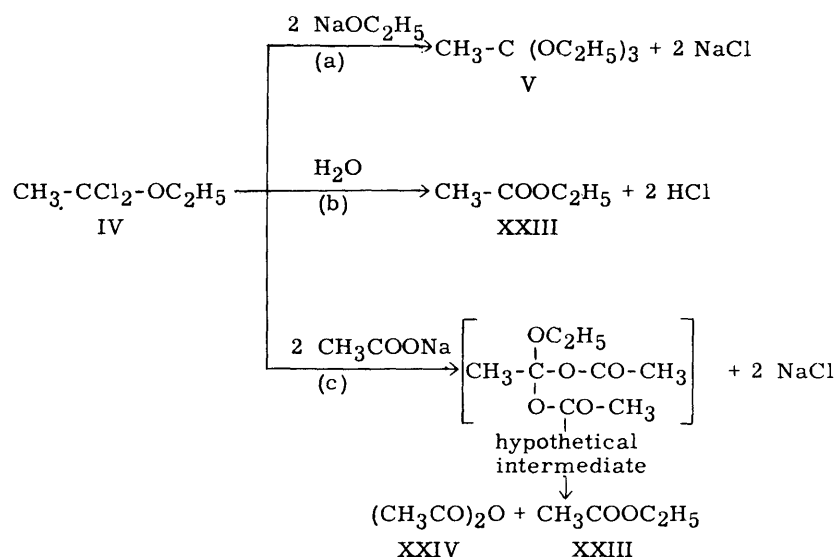
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Formation of α,α -dichlorodiethyl ether (IV) and its use for the preparation of acyl chlorides.

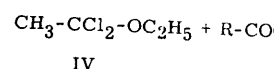
$$\text{HC}\equiv\text{C}-\text{OC}_2\text{H}_5 \xrightarrow{\text{HCl}} \text{H}_2\text{C}=\text{CCl}-\text{OC}_2\text{H}_5 \xrightarrow{\text{HCl}} \text{CH}_3-\text{CCl}_2-\text{OC}_2\text{H}_5$$

II
III
IV

b) By reaction with sodium acetate, acetic anhydride (XXIV) and ethyl acetate (XXIII) were formed in good yields:



At about 40°C the dichloro ether (IV) easily reacted with carboxylic acids, yielding acyl chlorides(XXV)and ethyl acetate (XXIII). In some cases the reaction already started at room temperature.

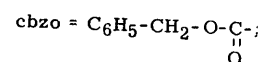
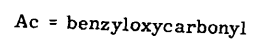
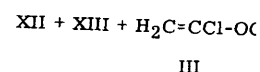
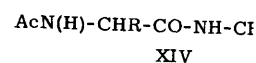
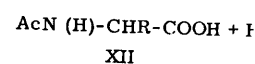


The use of the dichlorides of pure acyl chlorides and phosphorus chlorides must be considered as SOCl_2 , PCl_3 etc.

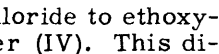
Synthesis of peptide

Two new methods for the synthesis of acyl peptide esters (I) from dry ethyl acetate and amino acid ester hydrolyzed ethers, α , α -dichloroethyl ether (III):

Reaction C: One step



The method has been of cbzo- and phth-di- In all experiments were isolated. Especially good results were obtained. The syntheses of a performed by heating


$$\text{3-CCl}_2\text{-OC}_2\text{H}_5$$

IV

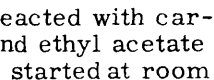
r (III) is a known

with b.p. 104.5-
ture of this com-
ons.

ol afforded ethyl-

anhydride (XXIV)

yields:

$$)_3 + 2 \text{NaCl}$$
$$+ 2 \text{HCl}$$
$$\left[\begin{array}{c} \text{O-CH}_3 \\ \text{CH}_3 \end{array} \right] + 2 \text{ NaCl}$$


In all experiments optically pure acyl peptide esters (XIV) were isolated. Especially with α, α -dichlorodiethyl ether (IV) good results were obtained.

The syntheses of a number of *phth* peptide esters were also performed by heating the reactants without a solvent. In these

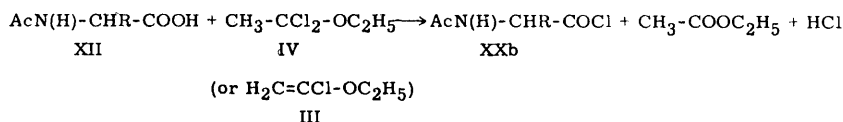
cases the reactions were very fast: reaction time 10-15 min.

Because of the known sensitivity of N-benzyloxycarbonyl-amino acyl chlorides (which most probably are intermediates) towards heat, this variation could not be applied for the analogous synthesis of N-cbzo peptide esters.

The various results are listed in tables IV, V, VIII, IX and X, (chapters II and III of this thesis, pages II-4, 5, 11, 12 and III-2.)

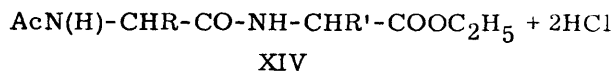
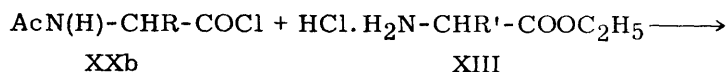
These new peptide syntheses most probably proceed as follows:

Reaction A: formation of N-acyl aminoacyl chloride (XXb).



Ac = N-protecting group (phth or cbzo).

Reaction B: formation of peptide bond.



These two steps (A and B) could also be performed separately.

Evidence for the occurrence of the acyl chloride (XXb) as an intermediate, during the synthesis of phth-gly-gly-Et with α, α -dichloro ether (IV) (reactions A, B and C) was obtained, by performing the reactions at 40°C and 77°C, and interrupting the processes before completion (see tables XI and XII, chapter III, pages III-7 and III-8 of this thesis).

Most probably, also in the peptide syntheses with ethyl α -chlorovinylether (III) these acyl chlorides (XXb) are intermediates.

Some free phth-peptides were obtained by refluxing a mixture of phth-aminoacyl chloride (XX) and free amino acid in ethyl acetate.

Of the two reagents for the synthesis of protected peptides, proposed here α, α -dichlorodiethyl ether (IV) is to be preferred.

The new method has the following attractive features:

- a) simple, "one step" procedures: isolation of intermediates is not necessary.
- b) short reaction times (0.5 - 1.5 h).
- c) good yields of optically pure N-acyl peptide esters.
- d) easy isolation of the crystalline reaction products.

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